Letter to the Editor

Bilirubin and migraine: critical review of the literature

Giuseppe Lippi[1], Camilla Mattiuzzi[2], Gianfranco Cervellin[3]

[1]Section of Clinical Biochemistry, University of Verona, Verona, Italy; [2]Service of Clinical Governance, Provincial Agency for Sanitary Services, Trento, Italy; [3]Emergency Department, University Hospital of Parma, Parma, Italy

Correspondence to: Prof. Giuseppe Lippi. Section of Clinical Biochemistry, University Hospital of Verona, Piazzale LA Scuro, 37134 Verona, Italy. Email: giuseppe.lippi@univr.it.

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We read with interest the recent article published by Peng *et al.* (1), who provided a comprehensive overview on the multiple clinical usefulness of measuring total bilirubin in serum or plasma. Among the various potential applications, the authors highlighted that total bilirubin was found to be lower in patients with migraine than in those without, a conclusion that was supported by a cross-sectional study published by the lead author of the review article (2). Since we believe that a single study, albeit scientifically sound, is not sufficient to draw definitive conclusions about this intriguing relationship, we carried out an electronic search on Medline (PubMed interface), Scopus and Web of Science using the keywords "migraine" AND "bilirubin", with no date or language restriction. The title, abstract and full text (when available) of all retrievable items were then scrutinized by two authors (G Lippi and C Mattiuzzi). The bibliographic references were also reviewed for identifying additional relevant studies. Only cross-sectional or prospective studies, containing precise sample size and total bilirubin test results (mean or median values and standard deviation or interquartile range) in patients with and without migraine were included in our analysis. The statistical analysis was carried out with MedCalc Version 12.3.0 (MedCalc Software, Mariakerke, Belgium). This was a personal study, based on a review of literature data, so that ethical committee approval was obviously unnecessary.

The final search allowed identifying 59 items after elimination of duplicates among the three scientific databases. Overall, 57 items were excluded for various reasons (a thorough discussion is omitted for space constraints). One additional article, not identified by the initial search, was retrieved so that our final analysis included three cross-section studies, averaging 527 patients (256 with migraine and 271 without). Inter-rater reliability was absolute (i.e., 100%).

The first identified study was published by Cao *et al.* in 2015 (3), and included 120 patients with migraine and 128 without. The total bilirubin concentration was found to be significantly lower in migraineurs than in the control population (*Table 1*). The second study was published by Peng *et al.* in 2016 (2), included 86 patients with migraine and 93 without, and also found that total bilirubin values were lower in patients with migraine than in those without (*Table 1*). Unlike these findings, the third identified study was published by George *et al.* in 2017 (4), included 50 patients with migraine and 50 without, and concluded that total bilirubin concentration was higher in migraineurs than in the control population (*Table 1*).

When data contained in these three separate cross-sectional studies were pooled, patients with migraine cumulatively displayed a significantly lower total bilirubin concentration than the control population [standardized mean difference, −1.31 µmol/L (95% CI, −1.98 to −0.64 µmol/L); P<0.001] (*Table 1*). Overall, total bilirubin concentration was found to be 12% lower (95% CI, −18% to −6%) in migraineurs than in subjects without migraine.

The many and multifaceted metabolic functions of bilirubin, the final product of heme metabolism, are still not completely understood. Several lines of evidence now attest that this molecule may produce both toxic and protective effects depending on its blood concentration. More specifically, lower values of total bilirubin in serum or plasma have been linked with an increased risk of developing cardiovascular disease (5), pulmonary

Table 1 Total bilirubin concentration in patients with or without migraine

Authors	Study population	Total bilirubin (μmol/L)		
		Migraineurs	Controls	P
Cao *et al.*, 2015	120 patients with migraine and 128 without	9.80±3.90	15.89±5.64	<0.001
Peng *et al.*, 2016	86 patients with migraine and 93 without	8.70±2.65	9.10±3.52	<0.001
George *et al.*, 2017	50 patients with migraine and 50 without	3.37±1.13	12.40±5.25	<0.001
Cumulative analysis	256 patients with migraine and 271 without	9.94±3.74	11.25±4.08	<0.001

embolism (6) and many other severe and prevalent human diseases (1). Interestingly, total bilirubin serum levels are also related with clinical severity of sudden event, such as carbon monoxide poisoning (7). Although it remains unclear whether total serum bilirubin acts as an active player or a bystander in many of these conditions, its measurement may provide useful information for the clinical decision making. In accordance with these earlier findings in other clinical settings, the results of our analysis more convincingly suggest that low total bilirubin concentration would also be associated with enhanced risk of migraine (*Table 1*). This epidemiological evidence is supported by a biologically plausible link. Bilirubin is a well-known endogenous antioxidant compound (5), whilst oxidative stress is strongly involved in the pathogenesis of migraine (8). It is hence conceivable that a low concentration of total bilirubin would be ineffective to prevent (or limit) the burden of oxidative stress, thus ultimately predisposing the development (or worsening) of migraine.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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